Review

Immunometabolism

OPEN

Macrophage metabolism impacts metabolic dysfunction-associated steatotic liver disease and its progression

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD), with a progressive form of metabolic dysfunction-associated steatohepatitis (MASH), is the leading chronic liver disease worldwide, which can progress to advanced liver disease and hepatocellular carcinoma. MASLD is tightly associated with metabolic disorders such as obesity, insulin resistance, and type 2 diabetes. Macrophages, as an innate immune component and a linker of adaptive immune response, play important roles in the pathogenesis and treatment of MASLD or MASH. Metabolic reprogramming can regulate macrophage activation and polarization to inhibit MASLD or MASH progression to advanced liver disease. Here, we summarize the underlying mechanisms of how different metabolites such as amino acids, glucose, and fatty acids can regulate macrophage function and phenotype, the factors that regulate macrophage metabolism, and potential treatment options to regulate macrophage function in MASLD or MASH, as well as other associated metabolic disorders.

Keywords: MASLD, MASH, macrophage, metabolism, molecular mechanism, clinical trials

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as metabolic dysfunction-associated fatty liver disease (MAFLD) or nonalcoholic fatty liver disease [1], has become the most common type of chronic liver disease worldwide, affecting more than a third of global adult population [2]. Metabolic dysfunction-associated steatohepatitis (MASH), also known as nonalcoholic steatohepatitis, is the progressive form of MAFLD with advanced liver inflammation, hepatocyte death, and varied degrees of liver fibrosis, which can progress to liver cirrhosis and hepatocellular carcinoma (HCC) [3]. Intrahepatic immune cells, including both innate and adaptive immune cells, play important roles in MASLD progression to HCC [4–6]. Kupffer cells, known as liver resident macrophages, are the largest population of hepatic immune cells and play important roles in MASLD and its progression to fibrosis, cirrhosis, and HCC [7,8].

Broadly, macrophages play important roles in systemic and local tissue inflammation, tissue repair, phagocytosis, and antigen-presenting function during pathogenic infection and chronic diseases [9–11], including MASLD and liver cancer. Tissue-resident macrophages (TRMs) can arise from yolk-sac erythro-myeloid progenitors during embryogenesis [12] and fetal monocyte progenitors [13]. In addition, monocyte-derived macrophages from bone marrow can also differentiate into TRMs during tissue injury [14]. Macrophages are plastic cells that can be classically polarized into M1 macrophages by stimulators such as lipopolysaccharide (LPS) from Gram-negative bacteria and interferon-γ (IFN-γ) and alternatively activated into M2 macrophages such as interleukin (IL)-4 and IL-13 [15]. M1 macrophages mainly produce pro-inflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-α (TNF-α), while M2 macrophages express anti-inflammatory cytokines such as IL-10 and transforming growth factor-β1 [16]. The functions of TRMs are largely dependent on the local environment. Macrophages such as tumor-associated macrophages (TAMs) [17], adipose tissue macrophages (ATMs) [18], and lipid-associated macrophages (LAMs) [19] are closely involved in the pathogenesis of diseases of cancer, obesity, and MAFLD/MASH, respectively. These findings suggest that macrophage phenotype and functions can be manipulated by the local microenvironment in diseases.

Cellular metabolism impacts macrophage function and phenotype, including the metabolism of fatty acids (FAs), amino acids, lipids, glucose, vitamins, and irons. M1 macrophages are mainly dependent on glycolysis with less process of tricarboxylic acid (TCA) cycle (Figure 1), while M2 macrophages rely mainly on mitochondrial oxidative phosphorylation (OXPHOS) [20]. Metabolic manipulation of macrophages is one of the strategies to alter their functions. For example, glycolysis mainly contributes to the pro-inflammatory function of ATMs in obesity, so metabolically rewiring ATMs may provide a novel therapeutic strategy [18]. In contrast, macrophage-derived metabolites such as glutamine can also impact other cell proliferation and differentiation [21]. Therefore, metabolically reprogramming TRMs can potentially recover or change the function of macrophages to defend against infection and mediate immune response in chronic disease.

In this review, we focus on the discussion of how the metabolic regulation of macrophages can impact the progression of MASLD to advanced liver disease. Some key important

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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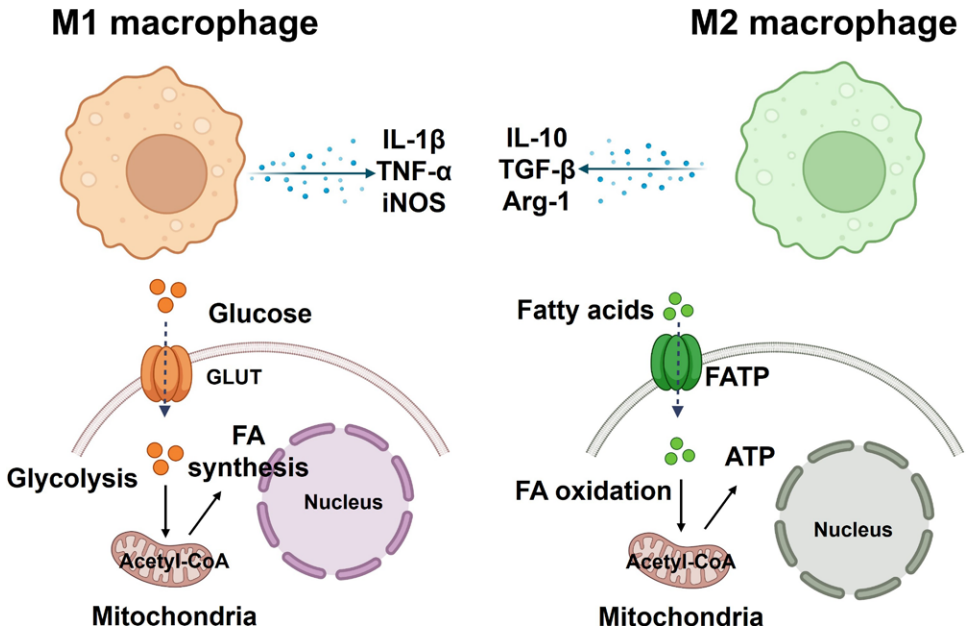

Figure 1. An overview of macrophage main energy metabolism. Activated macrophages are sub-classified into classically polarized M1 macrophages (pro-inflammatory) and alternatively activated M2 macrophages (anti-inflammatory). The glycolysis in M1 macrophages is increased. Glucose transporter proteins (eg, GLUT1) transport glucose into cells to undergo glycolysis to produce pyruvate that is metabolized to acetyl CoA through the tricarboxylic acid (TCA) cycle to produce excess citrate for de novo lipid synthesis. M2 macrophage mainly produces adenosine triphosphate (ATP) via the TCA cycle and oxidative phosphorylation (OXPHOS) fueled by fatty acid β-oxidation, with low glycolysis. Arg-1, arginase 1; FA, fatty acid; FATP, fatty acid transport; GLUT, glucose transporter protein; IL, interleukin; iNOS, inducible nitric oxide synthase; TGF-β1, transforming growth factor-β1; TNF-α, tumor necrosis factor-α. Cartoons were prepared by Biorender (https://biorender.com, accessed on January 1, 2024).

molecules or molecular signaling pathways are reviewed in this process. For the factors regulating macrophage metabolism, we give detailed information about the fatty acid transport proteins (FATPs). In addition, current clinical trials targeting macrophages to treat metabolic diseases are summarized.

2. Important metabolites involved in macrophage activation and inflammation in MASLD

In macrophages, metabolic alterations, such as glycolysis, glutamine synthesis, and lipid metabolism, impact their polarization to pro-inflammatory or anti-inflammatory phenotypes in vitro and in vivo [22]. Metabolites play important roles in liver health and pathogenesis. In this section, each category of metabolites involved in macrophage polarization and function in MASLD or MASH is discussed.

2.1 Amino acids

Arginine, as a substrate of 2 enzymes inducible nitric oxide synthase (iNOS) and arginase 1 (ARG1), has been used to define the M1/M2 dichotomy [23]. In contrast to M1 macrophages, M2 macrophages also display an intact functional TCA cycle and enhanced OXPHOS activity [23,24]. Glutamine metabolism orchestrates macrophage activation by involving in the TCA cycle. Production of α-ketoglutarate in glutaminolysis contributes to alternative activation of M2-like macrophages, favoring FA oxidation [24]. A study shows that deprivation of serine can reduce IL-1β production and metabolic profile in M1 macrophages, which is not able to be rescued by supplementation of formate, glucose, and deoxynucleotide triphosphates (dNTPs). In contrast, supplementation of glycine can rescue IL-1β production from serine-deprived macrophages, but not TNF-α production, which may be regulated by other signal pathways [25]. Serine can be metabolized into glycine to support LPS-induced expression of IL-1β in macrophages through glutathione synthesis [26].

Gut microbiota-derived metabolites of tryptophan, tryptamine, and indole-3-acetate (I3A) can inhibit palmitic acid and LPS-induced inflammation of macrophages. In addition, I3A is able to reduce free fatty acids (FFAs) and TNF-α-mediated lipid accumulation in hepatocytes by inhibiting FA synthase and the expression of sterol regulatory element-binding protein-1c [27]. Oral supplementation of I3A in mice with high-fat diet (HFD)-induced MASLD can significantly reduce hepatic lipid accumulation, hepatocyte ballooning, inflammation, and injury via inhibition of hepatic lipogenesis and activation of AMP-activated protein kinase (AMPK)-mediated anti-inflammatory function of macrophages [28].

2.2 Bile acids

Bile acids (BAs) regulate lipid and glucose metabolism and play important roles in the gut-liver axis [29]. The primary BAs are produced in the liver from cholesterol breakdown, which are transported to the intestine for producing secondary BAs by gut microbiota [30]. The ratio of primary and secondary BAs is altered in mice and humans with MASLD or MASH [31,32]. There are 2 well-known bile acid receptors, farnesoid-x-receptor and G protein-coupled bile acid receptor 1, which is also known as Takeda G protein-coupled receptor 5 (TGR5) [33]. Drugs that target BA receptors have been developed for the treatment of MASLD or MASH [34]. TGR5 deficiency increases liver injury and inflammation in mice with a normal chow diet or a methionine and choline-deficient diet and promotes M1 macrophage polarization by triggering nucleotide oligomerization domain (NOD)-like receptor protein 3 inflammasome activation and caspase-1 cleavage [35]. Similarly, another study reveals that TGR5-deficient macrophages show pro-inflammatory M1 polarization by upregulating cathepsin E gene expression, while TGR5 agonist enhances the anti-inflammatory effect of macrophages [36]. Studies also demonstrate that TGR5 is the major receptor that mediates the function of BAs on liver resident macrophages or Kupffer cells. Activation of TGR5 by agonist oleanolic acid (OA) can upregulate the expression of

pro-inflammatory cytokines IL-1β and TNF-α in Kupffer cells, which is regulated through c-Jun *N*-terminal kinase (JNK) signaling pathway [37]. In contrast, OA stimulation can significantly increase the expression of pro-inflammatory cytokines IL-1β and TNF-α in TGR5-deficient macrophages compared to wild-type Kupffer cells. Meanwhile, the expression levels of IL-1β and TNF-α are also increased in the livers of TGR5-deficient mice than normal livers of control mice when they are fed a 1% cholic acid diet [37]. These studies show that activation of TGR5 may simultaneously enhance both the anti-inflammatory and pro-inflammatory function of macrophages, but TGR5 deficiency can dramatically enhance the pro-inflammatory of macrophages. Taurolithocholic acid, a conjugated secondary BA, can regulate macrophage inflammation, phagocytosis, and immunoregulatory functions [38]. However, the specific roles of BAs on liver resident Kupffer cells and infiltrated monocytes or macrophages in MASLD or MASH remain to be further investigated.

2.3 Fatty acids

FAs, the common components of lipids, are essential nutrients and impact cell metabolism and function, with various structures such as triacylglycerols and phospholipids [39]. M1 macrophage polarization is associated with increased FA synthesis, while M2 macrophage polarization is associated with increased FA oxidation [40]. In the pathogenesis of MASLD or MASH, saturated FAs, especially palmitic acid, can impair the autophagy of macrophage via hypoxia-inducible factor 1 alpha (HIF-1α) to increase macrophage inflammation evidenced by upregulation of IL-1β production and nuclear factor (NF)-κB activation [41]. In human MASLD, genes involved in FA metabolism such as acyl-CoA synthetase long-chain family member 4 (*ACSL4*), fatty acid-binding proteins (eg, *FABP4* and *FABP5*), and lipoprotein lipase (*LPL*) are commonly upregulated besides genes that are involved in the recruitment of macrophages (monocyte chemoattractant protein 1, *MCP-1*, or *CCl2*) [42]. In addition, some proteins expressed on macrophages can regulate lipid uptake and accumulation in MASLD, such as macrophage scavenger receptor 1 (MSR1 or CD204) [43] and triggering receptors expressed on myeloid cells 2 (Trem2) [44]. In MASLD, TREM2-expressing macrophages localize in the inflammatory and fibrotic areas, playing important roles in the progression of liver fibrosis [45]. Similarly, MSR1 regulates lipid uptake and accumulation in hepatic macrophages or Kupffer cells, and blockade of MSR1 can prevent macrophage lipid accumulation in primary macrophages, mouse MASLD model, and human liver slices [43]. Thus, they are potential therapeutic targets for the treatment of MASLD.

The cluster of differentiation 36 (CD36) plays an essential role in the cellular uptake of FAs [46–48]. In the tumor microenvironment, TAMs express high levels of CD36 causing lipid accumulation, and mainly produce energy using FA oxidation instead of glycolysis, promoting tumor growth [49]. Meanwhile, tumor cells-derived lactate can further upregulate *ARG1* expression in TAMs to induce macrophage M2 polarization, which is mainly dependent on OXPHOS [50]. In contrast, LPS-activated M1 macrophages can shift metabolism from OXPHOS to glycolysis, increasing succinate (a 4-carbon FA) production. In addition, increasing mitochondrial oxidation of succinate can induce the production of mitochondrial reactive oxygen species (ROS) and pro-inflammatory cytokines (eg, IL-1β), while inhibiting succinate oxidation by inhibitor dimethyl malonate can promote anti-inflammatory cytokine (eg, IL-10) production [51]. Treatment with oleate, an unsaturated long-chain fatty acid (LCFA), can polarize human $CD14^+$ monocytes into $CD206^+$ immunosuppressive cells [52]. CD206 is a mannose receptor, which has been shown to be highly expressed by M2 macrophages and TAMs [52–54]. Treatment of eicosapentaenoic acid (EPA), an omega-3 FA, can inhibit macrophage polarization pro-inflammatory M1 phenotype, but not anti-inflammatory M2 phenotypes during the chronic cardiac remodeling stage after myocardial infarction [55]. Supplementation of EPA can significantly reduce HFD-induced increase of mouse body weight and adipose tissue weight and lower plasma insulin levels, as EPA can regulate liver and epididymal adipose tissue metabolites to inhibit macrophage inflammation [56]. EPA membrane incorporation can also inhibit cholesterol-induced macrophage foaming by reducing cholesterol efflux in these cells [57].

2.4 Glucose

Patients with MASLD or MASH have an increased chance of developing type 2 diabetes (T2D) [58]. The expression of soluble macrophage activation biomarker CD163 in patients with MASLD is associated with the levels of alanine aminotransferase (ALT) and homeostasis model assessment of insulin resistance [59,60]. The concentration of soluble CD163 is associated with glucose homeostasis and liver necro-inflammation in patients with MASLD [59], indicating the severity of MASLD [60]. Glucose plays an important role in macrophage inflammation and polarization. Overexpression of glucose transporter 1 (GLUT1) on macrophages can increase their uptake and metabolism of glucose, causing overexpression of ROS and pro-inflammation [61]. In the hypoxic environment, GLUT3 is overexpressed on macrophages to regulate glucose uptake and lipid accumulation [62]. This study also showed that the expression level of GLUT3, but not the expression levels of GLUT1, GLUT4, and GLUT5, was correlated with HIF-1α expression in response to hypoxia [62]. In contrast to glucose, D-mannose can inhibit LPS-induced macrophage M1 polarization by suppressing IL-1β expression in vitro and in vivo [63]. The reason causing this distinct effect of glucose and mannose is that treatment of mannose can impair glycolysis through glucose, which is important for LPS-induced IL-1β production in macrophages. Meanwhile, mannose is less efficiently metabolized via glycolysis than glucose in macrophages [63].

TAMs promote cancer progression by inducing immunosuppressive microenvironment, angiogenesis, and regulation of the infiltration of regulatory T cells (Tregs). For example, TREM-1-positive TAMs can impair the function of cytotoxic CD8 T cells and induce C-C motif chemokine receptor 6 $(CCR6)^+$ forkhead box P3 $(Foxp3)^+$ Treg accumulation by expressing programmed cell death ligand 1 (PD-L1) and chemokine (C-C motif) ligand 20 (CCL-20) [64]. Glucose is a major energy source of TAMs in the tumor microenvironment, and regulating glucose metabolism is a therapeutic strategy for cancer treatment, such as inhibition of glucose uptake and glycolysis inhibitor [65]. In addition, tumor cell glycolysis also impacts macrophage or antitumor immune cells in the immunosuppressive microenvironment, including aerobic and anaerobic (Warburg effect) glycolysis in HCC [66,67].

2.5 Irons

Disruption of iron metabolism and shift of macrophage polarization are positively associated with many metabolic diseases, such as obesity [68] and MASLD [69,70]. Iron overload can induce M1 polarization to increase the expression of IL-1β and TNF-α by inducing ROS production and p53 acetylation [71]. In vivo study shows that dietary iron overload can induce hepatic macrophage M1 polarization in C57BL/6 mice, resulting in fibrogenesis [72]. In addition, iron deposition in hepatic reticuloendothelial system cells can increase the expression of M1 macrophage markers, such as IL-6, IL-1β, and CD40, and decrease the expression of an M2 macrophage marker transglutaminase 2 (TGM2) in patients with MASLD [72].

2.6 Vitamins

Vitamin D receptors (VDRs) are highly expressed in liver macrophages. The activation of VDRs by vitamin D analog calcipotriol can ameliorate liver inflammation and fat accumulation and improve insulin sensitivity in obese mice [73]. Another study also shows that VDR-activated macrophages can suppress hepatic endoplasmic reticulum (ER) stress by reducing unfolded protein response in hepatocytes. In contrast, VDR deficiency can cause macrophage infiltration and increase the expression of pro-inflammatory cytokines [74]. Treatment with active vitamin D (1,25-dihydroxy vitamin D,1,25$(OH)_2$ D) induced M2 polarization of macrophages via upregulation of T-cell immunoglobulin-mucin-3 (Tim-3) expression in macrophages (RAW264.7 cells) [75]. The vitamin D/VDR signaling pathway in MASLD has been reviewed previously [74].

Intake of supplementation of vitamin E [76], vitamin A (provitamin A carotenoids) [77], and vitamin B12 [78] can improve the symptoms of MASLD to some extent. Treatment of vitamin E active forms such as α-tocopherol can reduce macrophage infiltration and reduce liver inflammation, apoptosis, and fibrosis in MASLD or MASH [79].

In conclusion, metabolically reprogramming macrophages can regulate their phenotypes and functions in MASLD or MASH (Table 1), as well as their production of cytokines.

3. Disease and transport proteins rewire macrophage metabolism

The local microenvironment in pathological conditions impacts the population and metabolism of macrophages [22,80]. Transporter proteins regulate nutrient uptake and metabolite transportation to mediate cell homeostasis in different pathological conditions [81,82].

3.1 Disease

Obesity, obesity-associated metabolic diseases, pathogenic infection, and tumor development impact macrophage function in MASLD to HCC progression.

3.1.1 Obesity and obesity-associated metabolic diseases

Obesity is positively associated with many metabolic diseases, such as T2D and cardiovascular disease, and MASLD [83,84]. Meanwhile, alteration of macrophage phenotypes and numbers happens in adipose and liver tissues during obesity. For example, macrophages are the main source of expression of TNF-α in adipose tissue during obesity, showing M1 phenotype with high expression of IL-6 and iNOS [85], while M2 macrophages are presented in lean subjects [86]. Increasing M2/M1 macrophage polarization in adipose tissue can decrease HFD-induced inflammation and insulin resistance in the liver and epididymal white adipose tissue [87]. MicroRNAs, small and highly conserved non-coding RNA molecules, are found to play an essential role in the regulation of macrophage gene expression by modulating metabolic and inflammatory signaling pathways [88,89]. For example, miR-130b was upregulated in macrophages that contributed to adipose tissue inflammation and insulin resistance by suppressing the expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) in HFD-induced obese mice [90]. Another study shows that miR-27a overexpression induced by HFD treatment in mice can promote M1 polarization of macrophages in adipose tissue by inhibiting PPAR-γ expression, resulting in insulin resistance and upregulation of pro-inflammatory cytokines [91]. In addition, mi-RNAs including miR-330-5p [92] and miR-495 [93] regulate macrophage M1/M2 polarization, contributing to insulin resistance in T2D in mice.

In obese tissue, adipocytes can communicate with macrophages. For example, a recent study shows that mitochondria can transfer intercellularly from neighboring adipocytes to macrophages in adipose tissue, which is dependent on the level of heparan sulfate [94]. This process regulates metabolic homeostasis in normal conditions, which is decreased in HFD-induced obesity.

3.1.2 Pathogenic infection

Macrophages express various pattern recognition receptors (PRRs) on the cell membrane to sense pathogen-associated molecular patterns (PAMPs) derived from microorganisms to trigger a rapid innate immune response to prevent microbial infections [95]. For example, many Toll-like receptors are

Table 1

Examples of metabolic regulation of macrophage functions in MASLD or MASH.

Metabolites	Group	Disease stages	Macrophage phenotypes and functions	References
Indole-3-acetate (I3A)	Gut microbiota-derived metabolite from tryptophan	MASLD	I3A activates AMPK-mediated anti-inflammatory function of macrophages.	[28]
Bile acids (BAs)	TGR5	MASLD/ MASH	Activation of TGR5 by agonist oleanolic acid can upregulate the expression of pro-inflammatory cytokines IL-1β and TNF-α in Kupffer cells, which is regulated by the JNK signaling pathway.	[37]
Palmitic acid (PA)	Saturated fatty acid	MASH	PA can activate HIF-1α to impair macrophage autophagy and induce macrophage inflammation by activating NF-κB and upregulating MCP-1 expression.	[41]
Glucose	Sugar	MASLD	The expression of soluble macrophage activation biomarker CD163 in patients with MASLD is associated with the levels of ALT and HOMA-IR.	[59,60]
Iron	Mineral nutrients	MASLD	Iron deposition in hepatic reticuloendothelial system cells can increase the expression of M1 macrophage markers, such as IL-6, IL-1β, and CD40, and decrease the expression of an M2 macrophage marker transglutaminase 2 (TGM2) in patients with MASLD.	[72]
Vitamin D	Vitamins	MASLD	The activation of VDRs by vitamin D analog calcipotriol can ameliorate liver inflammation and fat accumulation and improve insulin sensitivity in obese mice. VDR-activated macrophages can suppress hepatic ER stress by reducing unfolded protein response in hepatocytes. In contrast, VDR deficiency can cause macrophage infiltration and increase the expression of pro-inflammatory cytokines. Treatment with active vitamin D induced M2 polarization of macrophages via upregulation of Tim-3 expression in macrophages.	[73–75]

ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; ER, endoplasmic reticulum; HIF, hypoxia-inducible factor; HOMA-IR, homeostasis model assessment of insulin resistance; JNK, c-Jun *N*-terminal kinase; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NF, nuclear factor; Tim-3, T-cell immunoglobulin-mucin-3; TGR5, agonists of Takeda G protein-coupled receptor 5; VDRs, vitamin D receptors.

expressed in macrophage membranes to sense PAMPs to trigger inflammatory responses [96]. In addition to surface PRRs, some types of PRRs, such as NOD-like receptors and RIG-1-like receptors, exist in the cytoplasm, which can detect cytoplasmic pathogens to activate immune responses against infection [97]. Microbial infection can polarize macrophages into different phenotypes. For example, *Pseudomonas aeruginosa* infection can increase anti-inflammatory response to kill infected bacteria at an early stage, while apoptotic cells during the infection stage can stimulate anti-inflammatory cytokine production (eg, IL-10) in macrophages [98]. Similarly, macrophages can be polarized to either M1 (pro-inflammatory) or M2 (anti-inflammatory alternative) phenotype in viral infection [99], which can be regulated by viral pathogenicity and macrophage membrane receptors [100]. The activation of different PRRs in macrophages influences the expression of pro-inflammatory and anti-inflammatory cytokines [101].

3.1.3 Tumor microenvironment

TAMs, one of the most immune cells within tumors, increased the secretion of IL-1β under moderate hypoxic conditions due to increased stability of HIF-1α. Furthermore, under persistent and severe hypoxia, M2-like TAMs also secreted IL-1β induced by necrotic debris of HCC cells via activation of HIF-1α/IL-1β signaling loop [102]. M2-like macrophage in the tumor-adipose microenvironment was associated with poor survival of patients with breast cancer [103]. LAMs were found in a tumor-adipose junctional location with M2-like macrophage signatures and high expressing markers such as CD163 and osteopontin (OPN/SPP1) [103]. M1-like and M2-like TAMs coexist in the tumor microenvironment and show opposite effects, which are related to macrophage origin, activation status, and localization [104].

In chronic liver disease, macrophage function and phenotype change in different stages of liver pathogenesis from MASLD to HCC. The molecular markers of macrophages in MASLD or MASH, liver fibrosis, cirrhosis, and HCC have been investigated at single-cell level [105–108], such as LYZ, CD68, MNDA, C1QC, CD9, and TREM2. The expression of receptor-interacting protein kinase 3 (RIPK3) decreased TAMs in HCC, which is associated with hepatocarcinogenesis. The molecular study showed that RIPK3 deficiency promoted M2 polarization of TAMs, associated with activation of PPAR, increase of fatty acid oxidation (FAO), and reduction of ROS [109]. In addition, upregulating RIPK3 or inhibiting FAO can suppress HCC tumorigenesis by changing the TAM-mediated immunosuppressive microenvironment [109].

3.2 Transporter proteins

Many transporter proteins are associated with macrophage metabolism. Here, we use FATPs as an example to illustrate their role in macrophage functions. FATPs play pivotal roles in cellular metabolic homeostasis, which regulates the cellular flux of FAs in metabolic organs [110]. The FA uptake and oxidation in M1-like macrophages decrease compared to M2-like macrophages (Figure 1), while M1 macrophages have increased glycolysis and accumulation of triacylglycerol and cholesterol-rich lipid droplets [111,112]. The roles of FATPs in macrophage function and metabolism remain less explored. Here, we discuss some of the recent findings in this field, including the roles of FATP1-6 in macrophage polarization and metabolism in different microenvironments.

FATPs are a subfamily of the solute carrier transporter families (SLCs) that play important roles in immune cell metabolic reprogramming and cellular homeostasis [113]. FATP1-6, also known as solute carrier family 27 (SLC27)A1-6, and the family members mediate the update of LCFAs into cells [114,115]. For example, in the liver, the major proteins involved in the transport and trafficking of FFAs are FATP2 (SLC27A2) and FATP5 (SLC27A5) and the FA binding proteins (FABP1, 4, and 5) [116]. The expression of FATPs in different tissues is described in Table 2 [117].

3.2.1 FATP1

FATP1 is expressed in tissues where insulin can regulate LCFA uptake [126]. FATP1 depletion can increase glucose metabolism and amplify the pro-inflammation of classically activated macrophages (M1-like). HFD-fed mice lacking hematopoietic FATP1 ($FATP1^{B-/-}$) acquired more epididymal white adipose tissue with increased metabolic syndrome compared to controls ($FATP1^{B+/+}$) [127]. Oleate can stimulate FFAs and triglycerides (TGs) accumulation in macrophages via activating FATP1 and FATP2 expression but not FATP3 to increase FFA influx, which was attenuated by activating peroxisome proliferator-activated receptor alpha (PPAR-α) and PPAR-γ [118]. In addition, TNF-α treatment significantly decreased oleate-induced accumulation of total FFAs and TGs in macrophages via suppressing FATP1 expression but did not change the mRNA expression levels of other FATPs, including FATP2-4 [118]. FATPs also function similarly in endothelial cells. For example, in human adipose tissue microvascular endothelial cells, PPAR-γ can regulate the expression of FA uptake regulators including FATP1, CD36, and FABP4 [128].

3.2.2 FATP2

FATP2 has shown multifunctional roles in metabolic diseases, including MASLD, T2D, cholelithiasis, and chronic kidney

Table 2

The expression and functions of FATPs.

FATPs	Tissues [117]	Function
FATP1	White and brown adipose tissues, skeletal muscle, and heart	Upregulating inflammation, uptake of fatty acid, phosphorylation of JNK, regulated by PPAR-γ [118].
FATP2	Liver and kidney	Transport long-chain fatty acids (LCFAs), regulation in MDSCs by GM-CSF secreted by tumor cells in the tumor microenvironment [119,120]. FATP2 depletion decreases mouse body weight and serum triglyceride levels by increasing PPAR-α-regulated gene expression [121].
FATP3	Skin, heart, and adrenal gland	Expression of FATP3-5 is positively associated with activation of VAP-1 during hepatic steatosis and inflammation [122].
FATP4	WAT, BAT, small intestine, skin, heart, skeletal muscle, and brain	Knockdown of FATP4 increasing M2 polarization of THP-1-derived macrophages [123], regulating the activation of JNK/C-JUN signaling, regulated by PPAR-γ.
FATP5	Liver	Decreased expression of FATP5 is significantly and negatively associated with histological features of MASLD by regulating free fatty acid intake, including hepatocyte ballooning and fibrosis [124].
FATP6	Heart, breast	Transport of LCFAs, negatively associated with cardiac injury [125].

BAT, brown adipose tissue; FATP, fatty acid transport; GM-CSF, granulocyte macrophage-colony stimulating factor; JNK, c-Jun *N*-terminal kinase; MASLD, metabolic dysfunction-associated steatotic liver disease; MDSCs, myeloid-derived suppressor cells; PPAR-α/γ, peroxisome proliferator-activated receptor alpha or gamma; VAP-1, vascular adhesion protein-1; WAT, white adipose tissue.

Table 3

Treatment options by modulating macrophage function for diseases in pre-clinical and clinical trials.

Diseases	Treatment	Target or mechanism of action	Function	References
Obesity and type 2 diabetes	ω-3 polyunsaturated fatty acids (PUFAs)	Regulation of macrophage inflammation	ω-3 PUFAs decreased the expression of adipose tissue macrophage markers such as CCL2 and CD68, as well as diabetes biomarker netrin-1 in a randomized clinical trial.	[144]
Neoatherosclerosis	Berberine	Inhibition of macrophage inflammation	Berberine reduced oxidized low-density lipoprotein (ox-LDL)-induced macrophage activation and production of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 by suppressing galectin-3 via the NF-κB and AMPK signaling pathways in a Chinese clinical trial.	[145]
Gestational diabetes mellitus	BMS309403	FABP4 inhibitor	Treatment with BMS309403 significantly alleviated gestational diabetes mellitus (GDM) symptoms in mice by improving glucose and insulin tolerance inhibiting macrophage infiltration into the adipose tissues and transcriptionally suppressing the expression of TNF-α and IL-6. There was a positive correlation between the serum levels of FABP4 with insulin resistance and the expression of inflammatory cytokines TNF-α and IL-6 in GDM patients.	[146]
Breast cancer	Anti-IL-1β and anti-programmed cell death protein 1 (PD-1)	Immune regulation	Anti-IL-1β Ab treatment followed by anti-PD-1 Ab therapy completely abolished tumor progression in mice with breast cancers induced by orthotopic inoculation of 4T1 breast cancer cells.	[147]
Rheumatoid arthritis	Antagomir-155	miR-155 inhibitor	Monocytes from human rheumatoid arthritis patients showed a reduced ability to differentiate into M2-like macrophages, which is associated with miR-155 and TNF expression. Overexpression of miR-155 decreased M2 macrophage markers in healthy monocytes, and transfection of antagomir-155 in RA monocytes restored M2-like polarization.	[148]
Breast cancer	Propagermanium (PG)	CCL2 inhibitor	Treatment with the CCL2 inhibitor PG inhibited breast cancer cell metastasis in mice by suppressing the formation of premetastatic niches.	[149]
Atherogenesis	Leucine supplementation	Downregulation of lipid accumulation	Leucine supplementation in mice for 8 weeks can decrease cholesterol content in peritoneal macrophages by reducing the uptake of very low-density lipoproteins and triglyceride biosynthesis rate.	[150]
Type 2 diabetes	Vitamin D3 supplementation	Inhibition of CD36 expression	Vitamin D3 supplementation suppressed CD36 expression and oxidized LDL uptake in monocytes in patients with type 2 diabetes.	[151]
Obesity-associated cancer	Aerobic and resistance exercise	Inhibition of macrophage inflammation	A 16-week aerobic and resistance exercise intervention significantly decreased M1-like ATMs and increased M2-like ATMs, associated with an increase of anti-inflammatory cytokines such as adiponectin and a decrease of pro-inflammatory cytokines IL-6 and TNF-α in adipose tissue of obese postmenopausal breast cancer survivors in a randomized clinical trial.	[152]

AMPK, AMP-activated protein kinase; ATMs, adipose tissue macrophages; NF, nuclear factor.

disease. It not only can transport LCFAs as an FA transporter but also can activate LCFAs as a very-long-chain acyl-coenzyme A synthetase [119]. In the tumor microenvironment, granulocyte macrophage-colony stimulating factor (GM-CSF) secreted by tumor cells can induce the expression of FATP2 in myeloid-derived suppressor cells (MDSCs) by activating signal transducer and activator of transcription 3 (STAT3) signaling pathway [120]. GM-CSF can also induce FATP2 expression in polymorphonuclear MDSCs by activating the STAT5 signaling pathway [119]. Fatp2-deficiency mice with a regular chow diet had reduced weight gain, serum TG, and dietary FA absorption but had increased serum cholesterol levels compared to wild-type mice, affecting liver lipid metabolism mainly by increasing PPAR-α-regulated genes [121].

Global depletion of the *FATP2* gene in diabetic kidney disease-prone mice displayed a longer life span and improved kidney histopathology, glomerular filtration rate, and albuminuria compared to diabetic wild-type mice [129]. However, the depletion of *FATP2* did not impact the infiltration of macrophages in the kidneys of diabetic mice [129].

3.2.3 FATP3

The expression of FATP3 in the placentas of obese women was increased compared to lean women pre-pregnancy, which was associated with TG accumulation in placental tissue [130]. Increased expression of FATP3-5 was associated with activation of vascular adhesion protein-1 (VAP-1) during hepatic steatosis accompanying inflammation [122]. In macrophages, several FATPs can be regulated simultaneously. For example, the expression of FATP1-3 and FATP5 is increased in foam cells induced from THP-1-derived macrophages by lipid loading, which can be suppressed by overexpression of Nur77 (NR4A1, nuclear receptor subfamily 4 group A member 1) to enhance cholesterol efflux [131].

3.2.4 FATP4

LPS treatment slightly increased the mRNA expression of FATP4 and CD36 in mouse macrophage cell line RAW264.7 cells, whereas the expression of FATP1 was significantly suppressed, and no change was shown in the expression of FATP3, FATP5, and FATP6 [132]. Knockdown of FATP4 increased CD206 mRNA expression in THP-1-derived macrophages under M2-polarization (IL-4 or IL-4+IL-13 stimulation), while it suppressed LPS+IFN-γ-induced pro-inflammatory M1 phenotype, evidenced by decreased protein production of IL-6 and IL-8 [123]. In addition, FATP4 deficiency in bone marrow-derived macrophages from macrophage-specific FATP4-knockout mice alleviated tunicamycin-induced ER stress and pro-inflammation response [123].

3.2.5 FATP5

FATP5 is exclusively expressed in the liver. FATP5 depletion dramatically inhibited the uptake of LCFAs in hepatocytes, resulting in decreased hepatic TG and FFA content [133]. Decreased expression of FATP5 is significantly and inversely associated with histological features of MASLD, including hepatocyte ballooning and fibrosis, which is also associated with a reduction of liver fat accumulation [124]. FATP5 deficiency contributes to HCC progression and metastasis by increasing cellular glycolytic flux and ATP production via activation of the mammalian target of rapamycin signaling [134]. The function of FATP5 in liver macrophages remains to be clarified.

3.2.6 FATP6

FATP6 is highly expressed in the heart in response to LCFA uptake. The levels of CD36 and FATP6 were increased in cardiac tissue after hemorrhagic shock, which was associated with cardiac injury [125]. Bioinformatic analysis showed that the expression of FATP6 in non-tumoral breast tissue was increased compared with that in breast tumor tissue in clinic samples. In addition, suppressing FATP6 expression in non-malignant mammary epithelial cells inhibited FA uptake and cell proliferation [135]. Overexpression of FATP6 in human embryonic kidney 293 cells can increase the uptake of LCFAs. The function of FATP6 in heart macrophages remains unexplored.

In summary of the functions of FATPs, they play pivotal roles in inflammation, macrophage polarization, and MASLD (Table 2). The difference in FATP expression and function in tissues or organs may be caused by the difference in energy metabolism and parenchymal cell types of different tissues, as well as their substrate of transport.

4. Pre-clinical and clinical trials

Hepatic macrophages show different phenotypes in MASLD or MASH and its progression according to their molecular markers [136,137], such as CD11b, F4/80, CD68, CD32, CD206, endothelial cell-selective adhesion molecule (ESAM), C-type lectin domain family 4 member F (CLEC4F), and T-cell membrane protein 4 (TIM4). Macrophage-secreted inflammatory cytokines contribute to the pathogenesis of different chronic diseases [138], which is associated with the change in macrophage phenotype and metabolism. For example, annexin A5 treatment can shift the M1 to M2 polarization of hepatic macrophages by interaction with pyruvate kinase M2 (PKM2), resulting in improvement of hepatic steatosis, inflammation, and fibrosis in mice with MASH [139]. Treatment with docosahexaenoic acid, an omega-3 FA, can polarize macrophages toward an anti-inflammatory phenotype [140,141], which is associated with the reduction of serum inflammatory cytokines (https://clinicaltrials.gov/; NCT00885313) [142]. In addition, macrophage polarization can regulate hepatic progenitor cell response by upregulating the expression of Wnt3a [143]. Therefore, targeting macrophages is a therapeutic option for disease treatment.

Modulating macrophage cytokine production and phenotype can also be applied to treat other metabolic or chronic diseases. Some pre-clinical and clinical trials in the last 5 years are summarized in Table 3. The following studies are mainly included by involving the investigation of macrophage function or activation, different drugs, and metabolic disorders. The treatments include ω-3 polyunsaturated fatty acids (PUFAs, diet supplementation) [144], berberine (natural compound) [145], fatty acid-binding protein 4 (FABP4) inhibitor (small molecule) [146], immune regulation antibodies [147], targeting microRNAs (miR-155 antagonism) [148], targeting cytokine or chemokine expressed by monocytes or macrophages (CCL2 inhibitor) [149], leucine (amino acid) [136], vitamin D_3 (vitamin) [150,151], and exercise [152]. However, a phase 3 randomized clinical trial (ClinicalTrials.gov, trial number: NCT03028740) showed that treatment of cenicriviroc (CVC), a CCR2 and CCR5 receptor antagonist did not improve liver fibrosis in adults with MASH [153]. Therefore, new therapies and clinical trials are required in the future.

5. Summary

Macrophages can be classically activated into M1 macrophages and alternatively polarized into M2 macrophages with different microenvironmental stimuli. Although M1/M2 classification for macrophages is used in this review, Kupffer cells or liver resident macrophages can simultaneously express both M1 and M2 macrophage markers, and M1/M2 macrophages can be shifted with treatments such as omega-3 FAs [154,155]. Single-cell RNA sequencing data also show that classic M1/M2 classification has limitations in depicting liver macrophages [156]. Two different populations of macrophages display different patterns of metabolic profiles, including amino acids, glucose, lipids, iron, and vitamins. For example, FA uptake and oxidation in macrophages are altered during polarization. These metabolic profiles of macrophages are regulated by several molecular signaling pathways, such as FATP1-6. However, how these molecules modulate local TRM metabolic reprogramming and polarization is waiting to be further studied. In addition, targeting these molecules to regulate macrophage metabolism or cytokine production in MASLD or MASH is critically important, as well as other metabolic diseases. However, more pre-clinical and clinical trials are required to explore macrophage-mediated therapies in MASLD or MASH.

Author contributions

Conceptualization and data collection: MY and CZ; writing—original draft preparation, writing—review and editing: MY, SL, YS, and CZ. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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